CASE REPORTS

Refer to: Caggiano V, Nielsen SL, Glassy FJ, et al: Immunoglobulin D myeloma: Report of a case with unusual neurological complications. West J Med 134:153-158, Feb 1981

ABBREVIATIONS USED IN TEXT

BUN = blood urea nitrogen
Hb = hemoglobin
IgD = immunoglobulin D
RER = rough endoplasmic reticulum

Immunoglobulin D Myeloma

Report of a Case With Unusual Neurological Complications

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IMMUNOGLOBULIN D (IgD) myeloma, first described by Rowe and Fahey in 1965,[1] is rare and has several features which set it apart from other forms of multiple myeloma. The IgD myeloma protein is predominantly of the λ type, greater than 90 percent of patients with the disorder have Bence Jones proteinuria; extramedullary spread and amyloidosis are frequent and survival is short.[2] We report an additional case of IgD myeloma characterized by an aggressive clinical course, hepatosplenomegaly, renal insufficiency and neurological complications. Electron microscopic studies of bone marrow are also presented. Data from three other cases of IgD myeloma found in our laboratory are also presented.

Report of a Case

A 65-year-old man was well until three weeks before admission to Mercy General Hospital on December 20, 1976, when he noted the abrupt onset of severe midback, nonradiating pain. Admittance to hospital was eventually required because of increasing severity of the back pain.

On physical examination the following findings were noted: blood pressure 140/80 mm of mercury, pulse 96 beats per minute, temperature 37°C (98.6°F), respirations 14, height 165 cm (5 ft, 4 in) and weight 80 kg (176.8 lb). The patient appeared moderately ill and had severe back pain with minimal motion in bed. Midthoracic tenderness was present to mild percussion but no deformities or masses were noted. He had powerful strength in all four extremities and straight leg raising was negative. Deep tendon reflexes were symmetrically equal and full responses were obtained to pinprick, light touch, vibratory and position sense. Gait was not tested because of the patient's discomfort. The liver was felt 4 cm and the spleen 2 cm below the costal margins. No other abnormalities were noted.

Admitting laboratory data included the following: hemoglobin (Hb) 11.5 grams per dl; packed cell volume 33.0; leukocyte count 7,800 per cu mm, with 45 percent segmented neutrophils, 5 percent bands, 3 percent metamyelocytes, 2 percent myelocytes, 44 percent lymphocytes and 1 percent plasma cells; platelet count 118,000 per cu mm; blood urea nitrogen (BUN) 48 mg per dl; creatinine 3.8 mg per dl; SGOT (serum aspartate aminotransferase; formerly serum glutamic-oxaloacetic transaminase) 74 units; SGPT (serum alanine aminotransferase; formerly serum glutamic-pyruvic transaminase) 78 units; lactic dehydrogenase (LD) 418 units and total serum protein 5.7 grams per dl, with albumin 3.8 and globulin 1.9 grams per dl. Electrolytes, calcium, phosphorus, alkaline phosphatase and bilirubin levels were normal. A 24-hour urine collection showed excretion of 5.2 grams of protein. A monoclonal peak was identified in the beta region in both serum and urine by protein electrophoresis on paper and cellulose acetate. An IgD myeloma protein in the serum and free λ light chains in both serum and urine were identified by immunoelectrophoresis. Serum im-

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Submitted, revised, May 14, 1980.

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munoglobulin concentrations were as follows: IgG 211, IgA 13, IgM 7 and IgD 1,100 mg per dl.*

Extensive infiltration of bone marrow with plasma cells was noted on both aspirate smears and biopsy sections. Coagulation studies including bleeding time, prothrombin time, activated partial thromboplastin test, thrombin time and fibrinogen level were normal. Roentgenograms of the skeletal system showed multiple small lucencies of the skull and ribs, consistent with myeloma.

On the fourth hospital day the patient complained of numbness about the chin and mild blurring of vision in the left eye. Diminished facial sensation to pinprick and light touch around the point of the chin, covering an area of 4 cm in diameter and extending to the lower lip, and slight ptosis of the left upper eyelid were noted. Funduscopic examination, pupillary response, extraocular movements, visual fields to confrontation, speech, swallowing and mastication were normal. By the fifth hospital day the ptosis was more pronounced, diminished adduction of the left eye was apparent and horizontal diplopia was present. In addition to the apparent incomplete left third cranial nerve palsy, left mandibular motor and sensory dysfunction were also present, rather than an isolated mental nerve palsy, as initially suspected. There was deviation of the jaw to the left on opening the mouth, defective contraction of the left masseter muscle when the patient was asked to clench his teeth, and diminished to absent facial sensation in the distribution of the mandibular branch of the left trigeminal nerve. Computerized brain tomography showed only changes consistent with slight cortical atrophy and a technetium Tc 99m radionuclide brain scan showed no abnormalities. A myelogram showed a partial extradural block at the T3-T4 level. Unfortunately, the cerebrospinal fluid was not examined.

A treatment plan involving multiagent chemotherapy[3,4] and palliative radiation therapy to the thoracic spine and base of the brain was outlined, but the patient consented only to limited chemotherapy. Thus, on the sixth hospital day a four-day course of melphalan, 10 mg per M^2 per day and prednisone, 60 mg per M^2 per day was begun. No objective improvement was noted; instead there was progression of disease with decreasing renal function, increasing back pain, persistence of partial left third cranial nerve paralysis, left mandibular motor and sensory dysfunction and intermittent obtundation. The patient also had difficulty in voiding, and an indwelling catheter was required. Serum calcium levels and viscosity were normal, as were electrolytes. Transfusions of three units of red blood cells were required. On the 25th hospital day bilateral pneumonitis developed. At that time the Hb was 10.1 grams per dl, leukocyte count 2,900 per cu mm, with 48 percent neutrophils and platelet count 82,000 per cu mm. The BUN was 126 mg per dl and creatinine 13.4 mg per dl, the patient having also refused peritoneal dialysis, hemodialysis or plasmapheresis. Despite appropriate antibiotic therapy and careful attention to fluid and electrolyte management, his condition worsened and the patient died on the 29th hospital day.

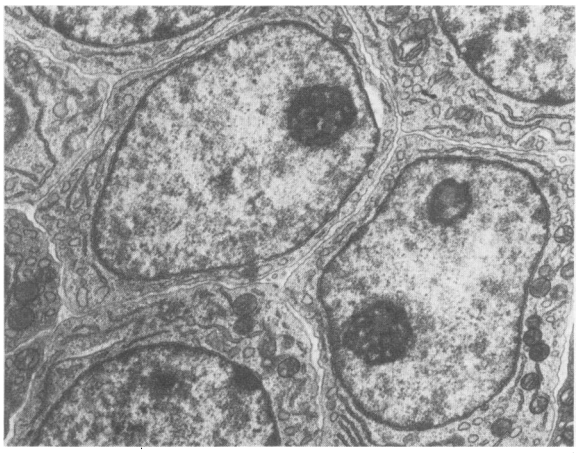

Figure 1.—Bone marrow electron micrograph. Primitive plasma cells containing large nucleoli, minimal fine nuclear chromatin and cytoplasm with distinct parallel bands of rough endoplasmic reticulum are identified. Mitochondria are seen in the right cell. The primitive nucleus and relatively well-developed cytoplasm are characteristic of nuclear-cytoplasm asynchrony. (Reduced from magnification ×6,300.)

Pathological Findings

Bone Marrow

Plasma cells made up 68 percent of all hematopoietic cells on bone marrow aspirate smears and biopsy sections as viewed under light microscopy. The majority were medium to large plasma cells with minimal cytoplasm and primitive-appearing nuclei with finely delicate chromatin with small or indistinct nucleoli. An occasional binucleate plasma cell was noted. The erythroid, myeloid and megakaryocytic series were morphologically normal.

Electron microscopic examination showed the

*The IgD quantitation was done by Hans L. Spiegelberg, MD, Department of Immunopathology, Scripps Clinic and Research Foundation, La Jolla, California..

bone marrow to consist predominantly of plasma cells with cytoplasm containing many parallel arrays of flattened rough endoplasmic reticulum (RER) and prominent Golgi apparati. Some of the cisternae of RER were dilated and contained a finely granular material of very light electron density. No crystalline material was seen. The nuclei had little chromatin aggregation and prominent nucleoli (Figure 1). These features indicated pronounced plasma cell nuclear-cytoplasmic asynchrony according to the criteria of Graham and Bernier.[5,6]

Postmortem Examination

Bronchopneumonia, pulmonary edema and pleural effusions appeared to be the terminal events. Widespread infiltrates of plasma cells were found in many sites including pleura, pericardium, liver, spleen, perirenal and periadrenal fat and retroperitoneal lymph nodes. Vertebral involvement was associated with extension into the epidural space, permeation of the dura and formation of a circumscribed intradural mass at the fourth thoracic level (Figure 2). Compression but not invasion of the spinal cord at this level corresponded to the mass lesion. There was extensive involvement of the sphenoid bone and cavernous sinus, especially on the left. Within the sinus, the infiltrate surrounded the venous channels, invaded the carotid artery adventitia and compressed cranial nerves (Figure 3). Involvement about the area of the left foramen ovale was not clearly observed. Petechial hemorrhages were noted in the brain stem and cerebrum as well as in soft tissues. Many renal tubules with compressed epithelial cells were dilated by eosinophilic amorphous material that contained elongated, eosinophilic, rod-like structures, suggesting a crystalline character. Nodular infiltrates of plasma cells were noted in the perirenal fat and fat of the renal pelvis. Amyloidosis was absent.

Discussion

Multiple myeloma has an annual incidence of about 3.0 per 100,000 population,[7] and IgD myeloma accounts for less than 3 percent of all myelomas.[2] To date, only 161 cases of IgD myeloma have been reported.[1,2,8-21] In the authors' experience at Mercy General and Sutter Community Hospitals from 1969 through 1979, 125 patients with plasma cell disorders were examined and four patients with IgD myeloma, one of them previously reported,[8] were identified (Table 1).

Neurological complications occur in over a third of patients with multiple myeloma, the most frequent abnormalities being nerve root pain, spinal cord or cauda equina compression, due either to extradural deposits of myeloma or collapsed vertebrae.[22] The patient described in the present report had vertebral involvement with extension into the epidural space, infiltration of the dura and formation of an intradural mass at the T4 level. Intracranial involvement is uncommon and generally presents in one of several forms—cases with myeloma deposits in the bone of the base of the skull, producing single or multiple cranial nerve palsies; cases simulating intracranial tumor syndromes, and cases with intraorbital involvement.[23] In one review, only two of 179 patients with myeloma (1.1 percent) had

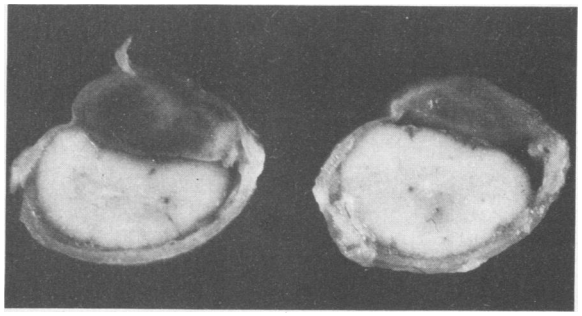

Figure 2.—Horizontal section of spinal cord at T4 level, showing distortion of the cord by the large intradural myeloma mass.

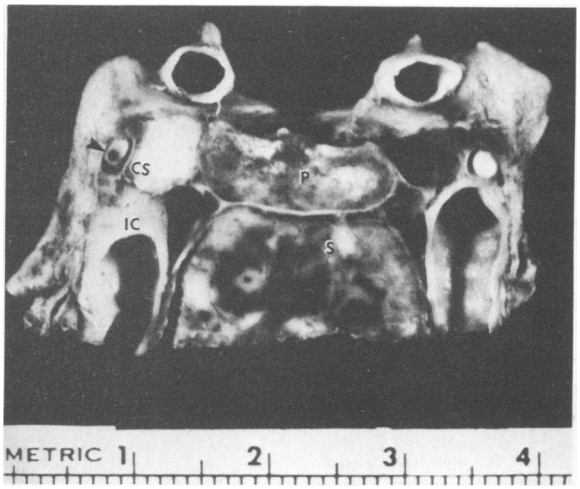

Figure 3.—Coronal section through the sella turcica and adjacent structures shows myelomatous infiltrates involving sphenoid bone and sinus (S), cavernous sinus (CS) and internal carotid artery sheath (IC). Lateral to the carotid, the infiltrate obscures the fourth, sixth and ophthalmic division of the fifth cranial nerves. Note the compression with focal hemorrhage of the left third cranial nerve (arrow). The pituitary (P) is uninvolved.

cranial nerve involvement.[24] Myeloma within the body of the sphenoid bone and in the apex of the petrous bone are the most common sites of involvement and the sixth, seventh, eighth and fifth cranial nerves most often afflicted, in that order.[23] In our patient, myeloma involved the sphenoid bone and the cavernous sinus. Within the latter, the infiltrate surrounded the vascular channels, invaded the carotid artery adventitia and compressed the cranial nerves. As others have commented, we cannot explain why the fourth and sixth nerves were spared.[25] The motor fibers of the fifth nerve pass with the mandibular branch, which does not traverse the cavernous sinus. However, compression of the nerve is possible along its course at the base of the skull, very probably in the region of the left foramen ovale. Isolated paralysis of the third nerve or the mandibular branch of the fifth nerve has been described in other patients with myeloma,[23,24,26] but to the best of our knowledge this combination of cranial nerve involvement, as clinically evident in our patient, has not been described. Direct arterial invasion by myeloma has been previously reported once, interestingly, in a case of IgD myeloma.[16]

Extramedullary spread of IgD myeloma has been noted in many sites, including the gastrointestinal tract, lymph nodes, liver, spleen, pleura, pericardium, genitalia, breasts, skin, skeletal muscles and heart. Involvement of kidneys was noted at autopsy in 19 of 33 patients with IgD myeloma described by Jancelewicz and co-workers,[2] and renal failure was the most common cause of death. The patient in the present report had extensive extramedullary spread of myeloma that included the kidneys, and the cause of death was renal failure complicated by pneumonitis. The single most important factor influencing prognosis is the level of the BUN or creatinine at the time of diagnosis.[27-29] Attempts to treat acute and chronic renal failure in patients with myeloma by peritoneal dialysis, hemodialysis and plasmapheresis have been successful.[29-32] Unfortunately, our patient did not consent to any of these forms of treatment.

The ultrastructural study of the bone marrow did not detect any abnormality specific for IgD myeloma. Most of the plasma cells had large nuclei, prominent nucleoli, well-developed endoplasmic reticulum, dilated cisternae and large Golgi areas. Pronounced nuclear-cytoplasmic asynchrony was observed both by routine light microscopy and electron microscopy.[5,6] Distinctive ultrastructural features of myeloma cells previously described[19,33,34] were not seen.

Certain patterns of clinical manifestation of multiple myeloma are related to the class and type of M component. Thus, hyperviscosity is most frequent in IgG3 myeloma,[35] the development of hypercalcemia is significantly more frequent in IgG2 myeloma,[36] the presence of λ-type Bence Jones proteinuria has an adverse influence on survival,[37] and myelomatous ascites is most often associated with IgA myeloma.[38]

A distinct clinical pattern of IgD myeloma has

TABLE 1.—*Cases of Multiple Myeloma (125) Seen at Mercy General and Sutter Community Hospitals (1969-1979)*

Class of M Component	Number of Cases: Light-Chain Type k	λ	Total	Percent
IgG	51	22	73	58.4
IgA	16	14	30	24.0
BJP	11	7	18	14.4
IgD	1	3	4	3.2
TOTAL	79	46	125	100.0

TABLE 2.—*Four Patients With IgD Myeloma Seen at Mercy General and Sutter Community Hospitals (1969-1979)*

Data	Patients 1*	2	3†	4
Age (yr), Sex	65, M	68, M	46, M	70, M
Survival (mo)	1.0	1.5	87.0	12‡
Admission BUN level (mg/dl)	48.0	117.0	22.0	16.0
Admission creatinine level (mg/dl)	3.8	7.1	0.7	1.0
Plasma cell asynchrony§	Pronounced	Pronounced	Slight	Slight
Light-chain type	Lambda	Lambda	Lambda	Kappa

BUN = blood urea nitrogen

*Patient described in present report.
†Patient reported previously.[8]
‡Patient still alive.
§Assessed by light and electron microscopy in patients 1 and 2, and by light microscopy only in patients 3 and 4.

also emerged. IgD myeloma represents an aggressive form of myeloma with a median survival of only nine months.[2,39] The total serum protein value is often low and the level of M component was lower than 2.0 grams per dl in 61 percent of reported patients, in clear contrast to the high levels of IgG and IgA M components.[2] In a review of 133 cases of IgD myeloma, the male to female ratio was 3:1; 65 percent of the patients were younger than 60 years at the time of diagnosis; more than half of the patients had lymphadenopathy, hepatomegaly or splenomegaly, and extraosseous spread and amyloidosis were frequent. Bence Jones proteinuria was found in 92 percent and Bence Jones proteinemia in 71 percent of the group.[2] In contrast to other forms of myeloma, the IgD myeloma protein was of the λ light-chain type in 90 percent of patients.

Our limited experience with four patients illustrates the variability of the clinical course of IgD myeloma (Table 2). In the absence of staging criteria for IgD, as have been developed for IgG, IgA and light-chain myelomas,[40] it seems reasonable to use the rating system devised for assessing clinical extent of disease and plasma cell asynchrony.[5] In agreement with Graham and Bernier,[5,6] the degree of asynchrony was proportional to the extent of disease as judged by clinical criteria.

Summary

A case of IgD λ myeloma characterized by Bence Jones proteinemia and proteinuria, hepatosplenomegaly, extensive extramedullary spread and renal failure with myeloma of the kidneys is presented. Unusual neurological complications included cranial nerve palsies that involved the left third nerve and the mandibular branch of the left fifth nerve. Extensive infiltration of the sphenoid bone with extension into the cavernous sinus was present. The pronounced nuclear-cytoplasmic asynchrony observed by both light and electron microscopy correlated with the extent and clinical aggressiveness of the disease. Because the level of the M component is often low and a monoclonal peak may not be apparent, the diagnosis of IgD myeloma may be overlooked unless appropriate application of immunoelectrophoresis is made to strengthen the clinical impression. Our community hospital experience confirms the usefulness of this laboratory procedure.

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Refer to: Ciferri F: Human pulmonary dirofilariasis in the West. West J Med 134:158-162, Feb 1981

Human Pulmonary Dirofilariasis in the West

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IN NATURE, the heartworm *Dirofilaria immitis* is transmitted primarily from dog to dog by mosquitoes carrying infective-stage larvae. In humans pulmonary dirofilariasis may develop when an infective larva is introduced into the abnormal human host, survives to become an adult filaria and then lodges in a branch of the pulmonary artery causing a small infarct. This is usually detected as a *coin* lesion in radiographs, surgical specimens or autopsies.

Fifty indigenous cases of this disease have been reported in the literature in the United States since its first description by Dashiell[1] in 1961. The geographic distribution of these cases (Figure 1) roughly parallels that of dog heartworm infection in this country.[2(pp1-2)] Most cases in humans have occurred along the Atlantic and Gulf coasts, from Massachusetts to Texas. This report describes the first documented case of human pulmonary dirofilariasis acquired in California and discusses its relationship to some of the epidemiologic factors that influence the transmission of this zoonosis to humans.

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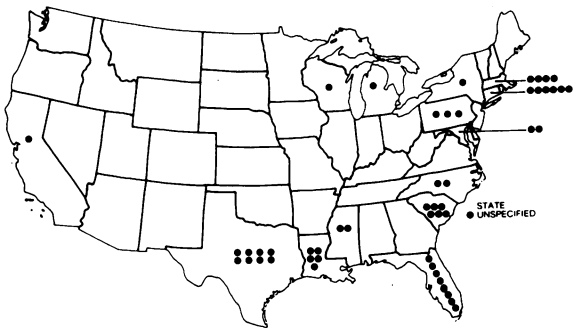

Figure 1.—Geographic distribution of human cases of pulmonary dirofilariasis in the United States, 1961-1979.

Report of a Case

A 67-year-old man, a retired machinist, was seen at our facility in Fontana, California, in September 1978 for a suspected prostatic malignancy. Except for the prostate, findings on the physical examination and the laboratory data were within normal limits. An x-ray study of the chest on September 9 showed no abnormalities. Needle biopsy of the prostate disclosed adenocarcinoma, stage IIIB. Surgical operation was declined, and the patient was treated with radiation from October 11 to December 8. He remained essentially asymptomatic—except for an eruption of herpes zoster on the left side of his chest on December 20—until January 12, 1979, when he reported that he had had a respiratory illness for ten days. It was characterized by coughing that produced whitish sputum, chest discomfort, malaise and fever. He was treated empirically with tetracycline for a week, but there was no symptomatic improvement. On January 22 a physical examination showed a temperature of 38°C (100.4°F) and bilateral moist rales; an x-ray study of the chest showed a 2-cm nodular lesion in the right lung field. He was treated with ampicillin for another week. There was symptomatic improvement, but the lung lesion remained unchanged. An extensive workup, which included tomograms, blood chemistry studies, sputum cytology, bronchoscopy, transbronchial biopsy and so on, failed to clarify the nature of this lesion. On March 12 a thoracotomy was carried out and the right lower lobe removed. At section, a firm, tan-white nodular mass measuring 1.8 × 1.5 cm was found, which on histologic examination contained several transverse sections of a sexually